

## A comparison between serum levels of interleukin-6 and CA125 in patients with endometriosis and normal women

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### Abstract

**Background:** The purpose of the present study was to compare the serum levels of IL6 and CA125 in women with and without endometriosis. They were also compared in mild, moderate and severe cases.

**Methods:** In this case-control study, CA125 and IL6 levels in 76 women with laparoscopic proven endometriosis were compared with 76 women without evidence of endometriosis. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were then calculated for each test.

**Results:** Both groups did not show significant difference in their age, BMI, ESR and gravidity. Mean serum levels of IL-6 and CA125 were significantly higher in the case group ( $30.4 \pm 6.43$  vs  $13.9 \pm 3.17$  Pg/ml and  $62.6 \pm 10.69$  vs  $16.6 \pm 1.79$  IU/ml respectively). Considering a cutoff point of 30 Pg/ml for IL-6, sensitivity, specificity, PPV and NPV value of 21.1%, 66.6%, 86.8% and 23.37% were obtained, respectively. Considering a cutoff point of 35 IU/ml for CA125, sensitivity, specificity, PPV and NPV were 44.76%, 94.73%, 89.47% and 63.15%, respectively. Area under the ROC curve was 0.69 for CA125 and 0.54 for IL6, which showed a low value for these tests.

**Conclusion:** Although CA125 and IL-6 were higher than normal controls in endometriosis, area under the ROC curve, did not show significant any diagnostic value for these tests.

**Keywords:** Endometriosis, Interleukin 6, CA125, Cytokines.

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### Introduction

Endometriosis is a progressive disease which consists of implantation of a combination of endometrial tissue including both stromal and glands outside the uterine cavity and may cause pelvic pain, severe intra-peritoneal adhesions and sub-fertility. It is more common in women who complain of chronic pelvic pain, dysmenorrhea and infertility (1,2). Standard diagnostic method for endometriosis is laparoscopic evaluation and histologic confirmation of findings. Laparoscopy is an invasive procedure (1) and needs hospitalization and anesthe-

sia. Ultrasound and MRI can help for the diagnosis of endometriosis too. Lack of non-invasive diagnostic methods leads to late diagnosis of endometriosis (3). Finding a noninvasive and simple method of diagnosis for evaluation of the women who are suspicious for endometriosis is always under serious concern. CA125 is a kind of cell surface antigen which is high in most cases of endometriosis, and has been proposed as a screening method for this disease. However, a meta-analysis on 22 studies, reported a very low diagnostic value for this test. (1,2).

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Serial measurement of CA125 may help for following up the patients after treatment (2). The cytokines including IL-6 have been proposed in the pathogenesis of endometriosis (4). IL-6 which is a multifunctional cytokine has been shown in a very high level in the peritoneal fluid of endometriotic women (5). Surgery for endometriosis may reduce the level of serum IL-6; it may decrease after GnRH agonist therapy (6). Interleukin-1 is a responsible cytokine in inflammatory and immunologic responses and is secreted from monocytes, activated macrophages, B and T lymphocytes and NK cells. It has been found in peritoneal fluid of endometriotic women and may cause activation of endometriotic tissue through releasing of angiogenic factors including IL6. In a study in 2002, IL6 was found higher in serum of endometriotic women. In this study (4), area under the ROC curve of 87% was calculated for serum IL-6. Other studies (3,6-9) showed similar results. In contrast, some studies could not show diagnostic or prognostic value for serum IL6 in endometriotic women (5,8-12). The purpose of the present study was to compare the serum level of IL6 and CA125 in the women with and without endometriosis. Moreover, they were compared in minimal to mild and moderate to severe cases.

## Methods

### Data

This case-control study was performed on women who underwent laparoscopy for their gynecologic problems including tubal ligation, abnormal uterine bleeding, infertility, pelvic pain, and ... in Rasool-e-Akram Teaching Hospital in Tehran, Iran, between March 2010 and March 2013. Serum levels of IL-6 and CA125 were measured in all women with and without the diagnosis of endometriosis and were compared between these two groups. Endometriosis was defined as minimal to mild if it was found on the surface of peritoneum and ovaries without deep and severe adhesions (1). Endometriosis was defined as moderate to severe

if it was invasive, with large endometriomas and deep and extensive adhesion according to AFS (American Fertility Society classification) scoring system (1). Inclusion criteria included women of reproductive age who were the candidate for laparoscopic evaluation of their gynecologic problems. Exclusion criteria included women with the diagnosis of acute pelvic inflammatory disease (PID) and vaginal discharge, women with any known history of inflammatory disorder or high erythrocyte sedimentation rate (ESR), neoplastic disorders, history of fever during past seven days, any medication for endometriosis during the last 3 months, laparoscopic findings of other pathologies except endometriosis in laparoscopy and elevated ESR. Laparoscopy was performed by two expert laparoscopic surgeons who made the diagnosis and staging of endometriosis. In this study considering  $\alpha = 0.05$  and  $\beta = 0.1$ ,  $OR=3$  a sample size of 76 women in each group was calculated. Seventy six women with confirmed diagnosis of endometriosis in laparoscopy were compared with women who had normal laparoscopic findings. Matching was performed according to the patients' age. Three mL of peripheral blood was collected in eligible women before laparoscopy and the serum IL-6 (ELISA, Bender Med, Canada) and CA125 (ELEXIS, Roche, Germany) were measured and compared between the groups.

### Statistical Analysis

The obtained data were analyzed using SPSS 16. Quantitative data was calculated as mean  $\pm$  standard deviation and qualitative data was calculated as numbers and percentages. Univariate analysis and chi-square test were utilized for comparing quantitative and qualitative data, respectively. Receiver operative characteristics (ROC) curve was used for determination of diagnostic value. P-value of less than 0.05 was considered significant. For maximum diagnostic value (sensitivity of 100% and specificity of 100%) and corresponding confidence intervals (CI), the area under

Table 1. Demographic characteristics of the women in each group

Characteristics	Control group (n = 76)	Case group(n = 76)	p
Age (year) M±SD	29.5 ± 6.8	29.5 ± 6.8	1
BMI M±SD	24.3±4.2	22.88±4.02	0.06
ESR M±SD	10.7±3.6	10.2±3.5	0.403
Gravidity			0.071
Single	6 (7.9%)	20 (26.3%)	
0	32 (42.1%)	29 (38.2%)	
1	15 (19.7%)	13 (17.1%)	
2	13 (17.1%)	9 (11.8%)	
≥3	10 (13.2%)	5 (6.6%)	

Table 2. Chief complaints of women in each group

	Control group (n= 76)	Case group (n= 76)
Abdominal pain n ( % )	22 (28.9%)	45 (59.2%)
Dysmenorrhea n ( % )	2 (2.6%)	11 (14.5%)
Infertility n ( % )	19 (22.4%)	35 (46.1%)
Abnormal uterine bleeding n ( % )	3 (3.9%)	9 (11.8%)
TL n ( % )	5 (6.6%)	0 (0%)
recurrent abortion n ( % )	3 (3.9%)	0 (0%)

the ROC curve is 1; and in the minimum diagnostic value, that the diagnosis is totally by chance, the area under the curve is 0.5.

## Results

A total of 152 women were evaluated by laparoscopy, including 76 women in endometriosis or case group, and 76 women in the control group. Mean age, gravidity, body mass index (BMI), and ESR did not show significant difference between the two groups (Table 1). Table 2 shows chief complaints of women in the each group; it shows significant difference ( $p= 0.001$ ). Mean serum levels of IL-6 and CA125

were higher in the case group (table 3). Serum level of IL-6 was not higher in minimal to mild endometriosis than control group; however, it was higher in moderate to severe endometriosis (Tables 4 and 5). Serum level of CA125 was higher in both minimal to mild and moderate to severe endometriosis than control group (tables 4 and 5). For a cutoff point of 35 IU/ml for CA125, sensitivity, specificity, PPV and NPV were 44.76%, 94.73%, 89.47% and 63.15%, respectively (Figure 1). For a threshold of 30 Pg/ml for IL-6, sensitivity, specificity, PPV and NPV were 21.1%, 66.6%, 86.8% and 23.37%, respectively (Fig. 2 and Table 6). Figure 1 and table 6

Table 3. Mean serum level of IL-6 and CA125 in each group

	Control group (n= 76)	Case group (n= 76)	p
IL-6 (Pg/ml)	13.98±3.17	30.42±6.43	0.048
M±SD			
CA125 (Iu/ml)	16.65±1.79	62.65±10.69	0.0001
M±SD			

Table 4. Mean serum level of IL-6 and CA125 in minimal to mild endometriosis and control groups

	Control group	Minimal to mild group	p
IL-6 (Pg/ml)	13.98±3.17	16.97±3.11	0.34
M±SD			
CA125 (IU/ml)	16.65±1.79	56.29±7.45	0.013
M±SD			

Table 5. Mean serum level of IL-6 and CA125 in moderate to severe endometriosis and control groups

	Control group	moderate to severe	p
IL-6 (Pg/ml)	13.98±3.17	32.12±6.74	0.034
M±SD			
CA125 (Iu/ml)	16.65±1.79	100.16±22.99	0.022
M±SD			

Table 6. Diagnostic accuracy parameters of CA125, and IL-6. (n=152)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	Accuracy (%)
CA125	44.76	94.73	89.47	63.15	69.7
CI 95%	(33.3 – 56.5)	(87.06 – 98.54)	(75.1 – 97.01)	(53.6 – 71.9)	(61.7 – 76.9)
IL-6	21.1	66.6	38.09	45.4	43.4
CI 95%	(12.5 – 31.9)	(54.1 – 76.29)	(23.5 – 54.3)	(35.9 – 55.2)	(35.4 – 51.6)

show the ROC curve of diagnostic value of CA125 for diagnosis of endometriosis with confidence intervals. The area under the curve is 0.69, and does not show significant value. Figure 2 shows the ROC curve of value of the IL-6 for prediction of endometriosis. Area under the curve is 0.54 and shows no significant diagnostic value.

## Discussion

In the present study both CA125 and IL-6 levels were higher in patients with endometriosis; however, CA125 level was high in both minimal to mild and mild to moderate endometriosis, and IL-6 level was higher just in moderate to severe cases. ROC curve showed low diagnostic value for IL-

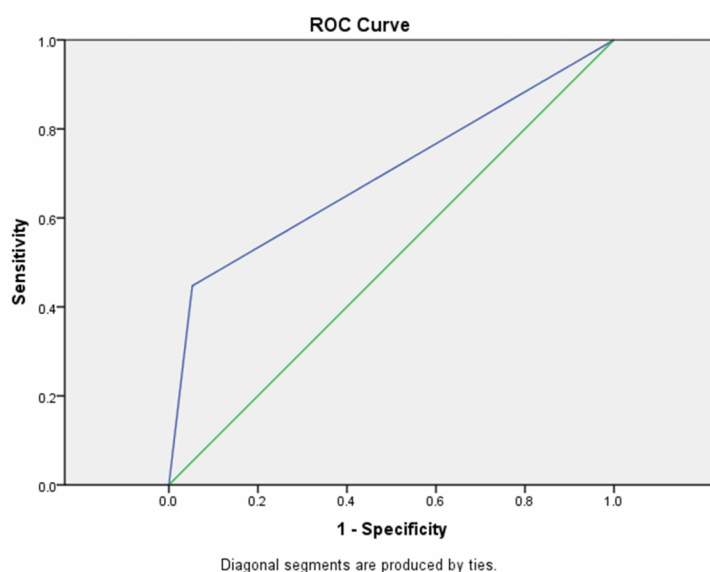


Fig. 1. ROC curve for CA125

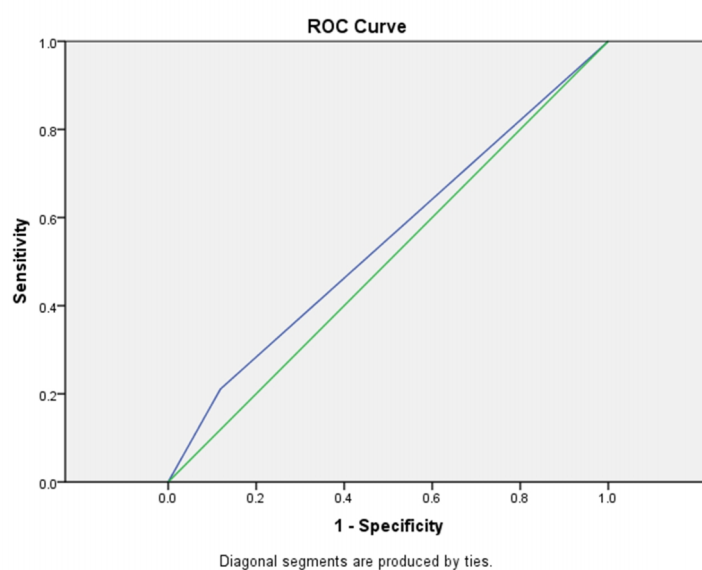


Fig. 2. ROC curve for IL-6

6; therefore it cannot be considered as a suitable diagnostic or prognostic test. IL-6 which is a multifunctional cytokine, has been shown in the peritoneal fluid of endometriotic women in a very high level (5). Surgery for endometriosis may reduce the level of serum IL-6, and it may decrease after GnRh agonist therapy (6). In a prospective study on 91 cases of endometriosis (4) who had been undergone laparoscopy, serum and peritoneal level of IL and other cytokines were evaluated. The researchers showed elevated serum level of IL-6 in endometriosis. Another studies (3, 8) showed similar results. Serum level of CA125 was higher in moderate to severe cases of endometriosis compared with minimal to mild cases (3). A case-control study on 68 endometriotic women and 70 normal women, reported higher serum level of IL-6 in endometriotic women which were in accordance with some other studies (6,7). Additionally, Martinez et al. (13) in a case-control study on 47 case of endometriosis and 72 normal cases, showed elevated level of IL-6 in endometriosis. In contrast, some other studies have questioned the value of serum IL-6 for diagnosis of endometriosis with this hypothesis that IL-6 was secreted by both ectopic and utopic endometrial stromal cells (5,9). on the other hand, some studies could not show higher level of IL-6 in endometriosis than normal women (11,12); they proposed that IL-6 cannot add more information than CA125 for the management of endometriosis (10). Another study on 13 women could not show significant difference between serum and peritoneal fluid IL-6 level in women with deep endometriosis and superficial endometriosis (10,12)

### Conclusion

Considering controversies between our results and also within previous studies, it is suggested that more studies to be performed on cases with various severities of endometriosis before proposing a definitive

conclusion.

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